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CLINICAL LIVER

Bariatric Surgery Provides Long-term Resolution of Nonalcoholic Steatohepatitis and Regression of Fibrosis

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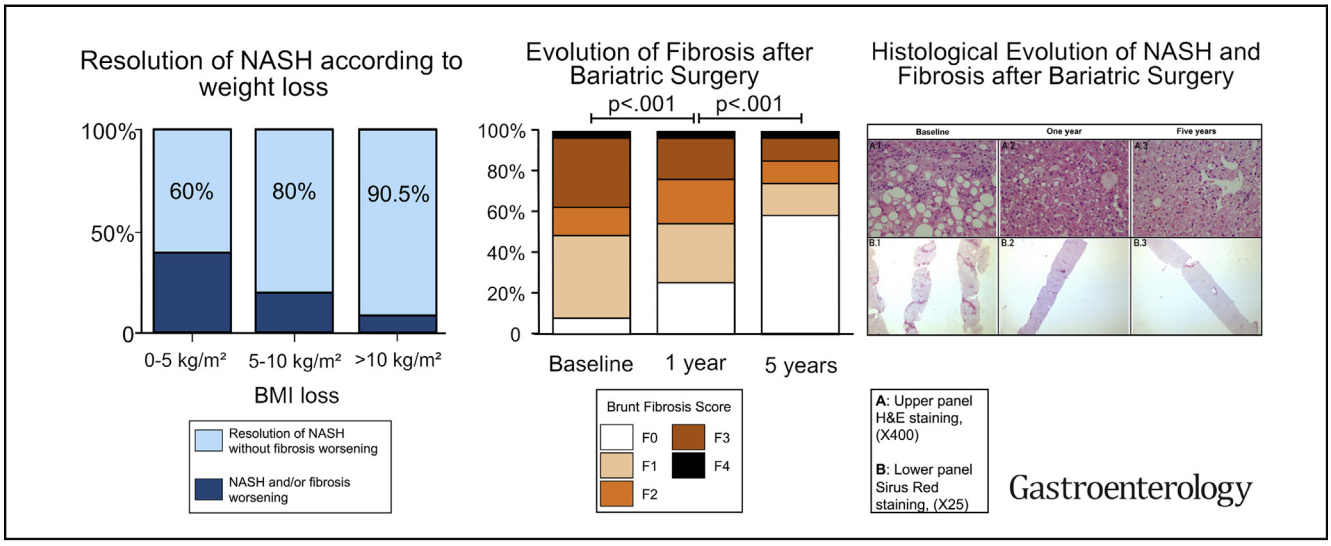

See Covering the Cover synopsis on page 1193.

BACKGROUND AND AIMS: Studies are needed to determine the long-term effects of bariatric surgery for patients with nonalcoholic steatohepatitis (NASH). We evaluated sequential liver samples, collected the time of bariatric surgery and 1 and 5 years later, to assess the long-term effects of bariatric surgery in patients with NASH. **METHODS:** We performed a prospective study of 180 severely obese patients with biopsy-proven NASH, defined by the NASH clinical research network histologic scores. The patients underwent bariatric surgery at a single center in France and were followed for 5 years. We obtained liver samples from 125 of 169 patients (76%) having reached 1 year and 64 of 94 patients (68%) having reached 5 years after surgery. The primary endpoint was the resolution of NASH without worsening of fibrosis at 5 years. Secondary end points were improvement in fibrosis (reduction of $\geq$1 stage) at 5 years and regression of fibrosis and NASH at 1 and 5 years. **RESULTS:** At 5 years after bariatric surgery, NASH was resolved, without worsening fibrosis, in samples from 84% of patients (n = 64; 95% confidence interval, 73.1%-92.2%). Fibrosis decreased, compared with baseline, in samples from 70.2% of patients (95% CI, 56.6%-81.6%). Fibrosis disappeared from samples from 56% of all patients (95% CI, 42.4%-69.3%) and from samples from 45.5% of patients with baseline bridging fibrosis. Persistence of NASH was associated with no decrease in fibrosis and less weight loss (reduction in body mass index of 6.3 ± 4.1 kg/m^2 in patients with persistent NASH vs reduction of 13.4 ± 7.4 kg/m^2; $P = .017$ with resolution of NASH). Resolution of NASH was observed at 1 year after bariatric surgery in biopsies from 84% of patients, with no significant recurrence between 1 and 5 years ($P = .17$). Fibrosis began to decrease by 1 year after surgery and continued to decrease until 5 years ($P < .001$). **CONCLUSIONS:** In a long-term follow-up of patients with NASH who underwent bariatric surgery, we observed resolution of NASH in liver samples from 84% of patients 5 years later. The reduction of fibrosis is progressive, beginning during the first year and continuing through 5 years.

Keywords: Gastric Banding; Gastric Bypass; Roux-en-Y-Gastric-Bypass; Sleeve Gastrectomy.

Abbreviations used in this paper: **APRI, aspartate aminotransferase-to-platelet ratio index; BMI, body mass index; CI, confidence interval; IQR, interquartile range; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD Activity Score; NASH, nonalcoholic steatohepatitis; QUICKI, quantitative insulin sensitivity check index.**

Most current article

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The global threat of obesity and the metabolic syndrome explain the growing public health burden of nonalcoholic fatty liver disease (NAFLD) worldwide. In the past 10 years, NAFLD has become the second cause of hepatocellular carcinoma and the third cause of decompensated cirrhosis on the transplant list in the United States.[1]

Nonalcoholic steatohepatitis (NASH) represents the severe and inflammatory phenotype of NAFLD and has the highest risk of disease progression to cirrhosis.[2] Thus, experts recommend targeting therapeutic developments in NASH patients to reduce the risks of morbidity and mortality.[3]

Sustained weight loss through lifestyle changes, including diet and physical activity, is the first step of therapeutic management according to international NASH guidelines.[4,5] Indeed, weight loss enhances liver and peripheral insulin sensitivity, reduces oxidative stress, and improves the lipid profile. Weight loss of at least 7% to 10% is necessary for the regression of NASH.[6,7] However, only 10% of patients reach this objective with lifestyle therapy at 1 year, and fewer than half maintain the weight loss 5 years later.[8]

Thus, an increasing number of clinical trials are evaluating novel molecules that focus on the multiple pathways involved in the pathogenesis of NASH. However, despite positive results in phase II and III studies, for the moment, no drugs have been approved for this disease.

Parallel to pharmaceutical development, bariatric surgery is an attractive option in severely obese patients. Bariatric surgery induces long-term weight loss (15%–25%) and remission of diabetes, while also reducing long-term mortality, cardiovascular events, and cancer. [9–15] Bariatric surgery results in a significant short-term improvement in steatosis, which is closely connected with the progression of insulin resistance.[16] Bariatric surgery induces the resolution of NASH in approximately 80% of patients at 1 year, but the long-term impact is still unclear because there are no large studies in NASH patients.[17] The only available long-term results come from studies in patients with mild NAFLD lesions, showing a sustained decrease in liver fat and probable improvement in necroinflammatory features.[18]

In addition to the resolution of NASH, medical agencies and expert panels consider a decrease in the extent of fibrosis to be a key end point for the reduction of liver mortality and morbidity.[3] The effect of bariatric surgery on the progression of fibrosis is a subject of debate. Indeed, the worsening of fibrosis is a major concern since a report on the development of cirrhosis 5 years after surgery in a historical study of ileojejunal bypass, a procedure that is no longer used.[19] More recently, a short-term decrease in fibrosis was observed in NASH patients.[17]

Although the largest prospective cohort study of patients with mild NAFLD reported a risk of the worsening of fibrosis at 5 years, the study is frequently misinterpreted.[18] First, the worsening of fibrosis at 5 years was slight, and the fibrosis score of 95% of patients 5 years later was $\leq$F1. Also, most patients (>90%) did not have NASH. Obviously, the low percentage of extensive fibrosis at baseline in this study prevented the risk of significant worsening, and the lack of baseline NASH makes it impossible to draw any firm conclusions. Thus, new long-term prospective data in a population of NASH patients with fibrosis are clearly needed. Based on this, we performed a prospective study with long-term follow-up to analyze the evolution of NASH and fibrosis including consecutive liver biopsies at 1 and 5 years.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Little is known about the long-term effects of bariatric surgery for patients with nonalcoholic steatohepatitis (NASH).

NEW FINDINGS

In a long-term follow-up of patients with NASH who underwent bariatric surgery, NASH resolved in liver biopsies from 84% of patients 5 years later. The reduction of fibrosis began during the first year and continued through 5 years.

LIMITATIONS

This study was performed in a single cohort of patients with severe obesity.

IMPACT

Bariatric surgery is an effective treatment for NASH in severely obese patients.

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Methods

Outcomes

The primary outcome of our study was the resolution of NASH with no worsening of fibrosis 5 years after surgery. The secondary outcomes were (1) improvement in fibrosis (reduction of $\geq$1 stage) at 5 years, and (2) progression of NASH and fibrosis, compared with baseline, at 1 and 5 years. Fibrosis stage 1a, 1b, and 1c were considered to be stage 1 for the statistical analysis. Other secondary outcomes included changes from baseline to 5 years in serum aminotransferase, γ-glutamyltranspeptidase, serum triglycerides, total cholesterol, fasting blood glucose concentrations, and anthropometric measures of weight and body mass index (BMI). Insulin resistance was assessed with the quantitative insulin sensitivity check index (QUICKI) that was calculated as follows: QUICKI: 1/(log fasting insulin)(log fasting plasma glucose). The insulin resistance index is equal to 1/QUICKI.

Patients

Between 1994 and June 2017, severely or morbidly obese patients were referred to our bariatric surgery unit for evaluation for bariatric surgery. Patients who fulfilled the following criteria for bariatric surgery were prospectively included in the Lille bariatric cohort on the day of the surgical procedure. Patients were:

1. 18 years or older at the time of evaluation and fulfilled the criteria for bariatric surgery according to French national guidelines;

2. had been morbidly (BMI >40 kg/m^2) or severely obese (BMI >35 kg/m^2), with at least 1 comorbidity factor (eg, arterial hypertension or diabetes mellitus), for at least 5 years and were resistant to medical treatment;
3. had no medical or psychologic contraindications to bariatric surgery;
4. had French health insurance coverage;
5. did not drink excessively, defined as an average daily consumption of alcohol of 20 g/d for women and 30 g/d for men, and had no history of excessive drinking for a period longer than 2 years at any time in the past 20 years;
6. had no history of long-term consumption of hepatotoxic drugs, and;
7. screened negative for chronic liver disease.

In June 2017, the Lille bariatric cohort included 2616 patients. We excluded 11 patients for a history of excessive alcohol consumption before or after bariatric surgery, 2 who had hepatitis B, and 64 other patients who did not have a baseline liver biopsy. Two of the excluded patients for a history of alcohol consumption died of alcoholic hepatitis or alcohol-related complications. Patients with potential confusing bias for hepatotoxin (ie, tamoxifen use for breast cancer) did not undergo follow-up liver biopsy.

Among the cohort, 189 patients had a pathology-based NASH diagnosis, and 9 patients were excluded from analysis due to the poor quality of the liver specimen (sample size of <6 portal triads or length <8 mm). Thus, 180 patients with NASH were included and prospectively monitored for 5 years after baseline (see the flowchart in Figure 1).

Informed written consent was obtained from all patients, and the study was performed in accordance with the Declaration of Helsinki. The ethics committee approved the cohort. After legal revision, new approval was obtained in 2006 (no. CP06/49; NCT01129297).

Surgical Procedures

The indication for bariatric surgery was confirmed after an extensive preoperative multidisciplinary evaluation according to current French guidelines. All patients followed a nutritional program before surgery. This program began with a multidisciplinary evaluation (nutritionist, psychologist, dietician, and therapeutic education nurse) to adapt preoperative care according to the patient's profile. In addition, all patients were required to undergo outpatient follow-up and to participate in a therapeutic education program for 6 to 12 months before surgery. At the end of this program, a multidisciplinary evaluation was again performed to validate and schedule the surgery.

The type of surgery was then chosen by the patient after she or he received comprehensive information about the various available surgical procedures, their specific risks, and expected results. From 1994 to 2001, only biliointestinal bypass and gastric banding were proposed. After 2001, gastric bypass was performed. Starting in 2004, biliointestinal bypass was no longer performed and was replaced by gastric bypass. The second bariatric procedure included an adjustable gastric band inserted by laparoscopy (Lap-Band System; INAMED Health, Santa Barbara, CA). The third procedure was Roux-en-Y gastric bypass, which involved partitioning the upper stomach to create a small gastric pouch, and gastrojejunostomy to re-establish gastrointestinal continuity. The final procedure consisted of sleeve gastrectomy and has been performed since 2006. The rate of gastric bypass was stable during the study period. At 1 year after the introduction of sleeve gastrectomy, the use of gastric banding was gradually replaced and reduced from 33% to 10% of the surgical procedures, whereas sleeve gastrectomy increased from 5% to 17%.

Histologic Analysis

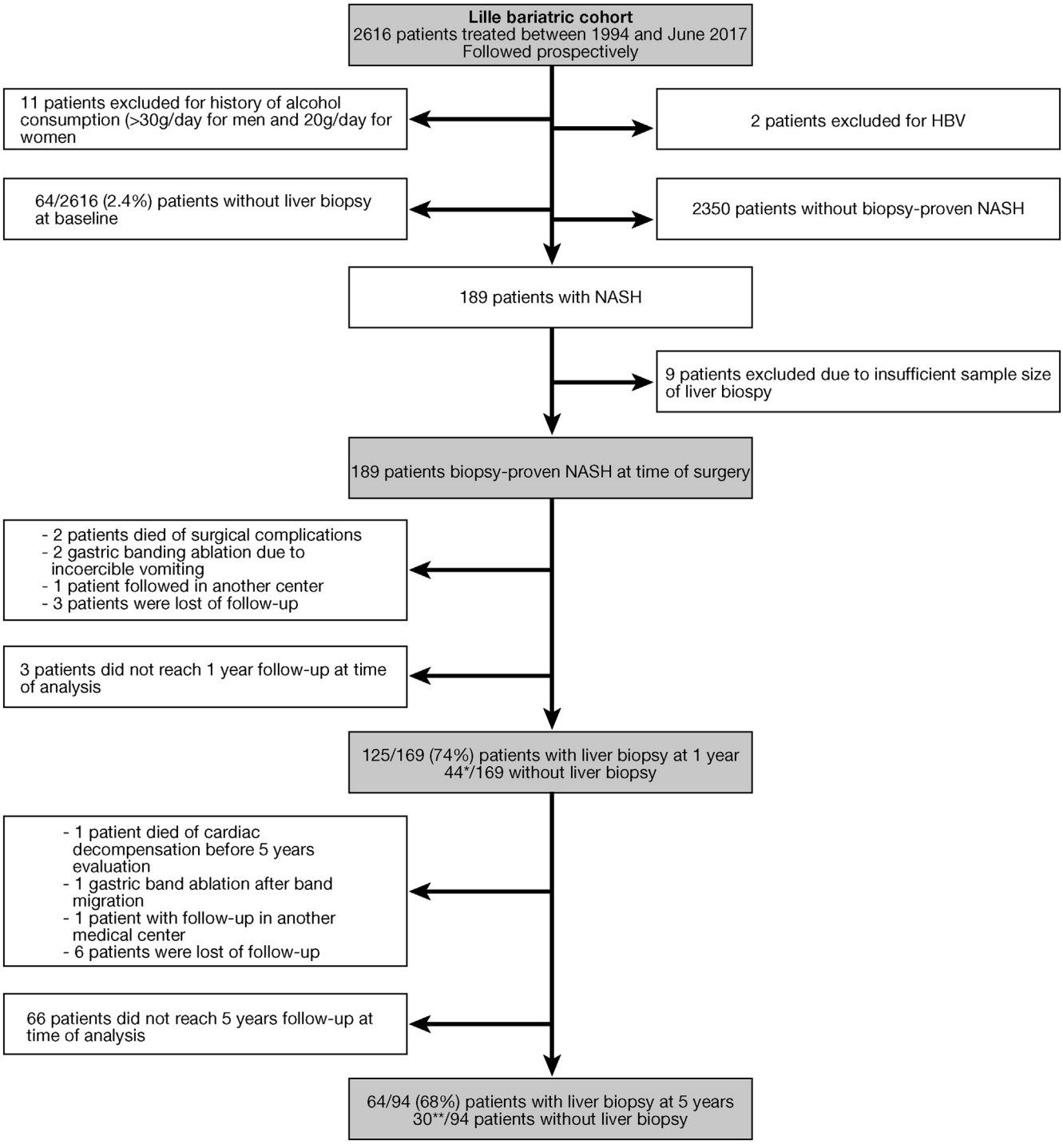
Liver biopsies were systematically planned during the surgical procedure and were performed in 2552 patients (97.6%), but not in 64 for miscellaneous reasons. A histologic assessment was planned approximately 1 year and 5 years after surgery. To avoid artifacts related to prolonged exposure of the liver, liver needle biopsy was performed during the first part of the surgical procedure after trocar insertion and abdominal exploration, within 10 minutes after pneumoperitoneum installation. The Hepafix needle biopsy system (B.Braun Medical; Melsungen, Germany) was used until 2010 and the MONOPTY needle biopsy system (16-gauge, ref: 121620; C.R. Bard, Tempe, AZ) thereafter.

Liver specimens were routinely stained with H&E saffron, Sirius red, and Perl's staining. Steatosis was quantified by the percentage of hepatocytes containing fat droplets (amount of steatosis). The pathologists (E.L., V.G., B.B., and D.B.) first diagnosed NASH, then determined the NAFLD Activity Score (NAS) and graded the severity of necroinflammatory activity using the Brunt's score. [20,21] which is defined by a 3-step scale: mild, grade 1; moderate, grade 2; and severe, grade 3. The NAS score, defined as the unweighted sum of scores for steatosis (0–3), lobular inflammation (0–3), and ballooning (0–2), ranging from 0 to 8, was also evaluated for the histologic follow-up of NASH after bariatric surgery. [22,23] Because the Brunt's and NAS scores were developed and published in 1999 and in 2005, respectively, all the liver specimens performed before 2005 were reviewed and graded retrospectively.[17,18] After 2005, all biopsy specimens were graded prospectively with these 2 scores, and results were standardized in a report. Pathologists were blinded to clinical and biological data.

Liver fibrosis was assessed semiquantitatively using Kleiner's fibrosis score, defined as follows: F0, normal; F1 stage is divided into 3 subclasses: 1a, mild pericellular fibrosis in zone 3, 1b, moderate pericellular fibrosis in zone 3, and 1c, portal fibrosis; F2, perivenular and pericellular fibrosis confined to zones 2 and 3, with or without portal or periportal fibrosis; F3, bridging or extensive fibrosis with architectural distortion and no clear-cut cirrhosis; and F4, cirrhosis.[23] For inclusion in the histologic analysis of specimens from consecutive liver biopsies, liver samples had to be at least 8 mm long or contain at least 6 portal triads.

Statistical Analysis

Continuous variables are expressed as means ± SD in case of normal distributions or as medians and the interquartile range (IQR) otherwise. Normality was examined using histograms and the Shapiro-Wilk test. Ordinal (semiquantitative scores) and nonordinal categorical variables are expressed as


Lille bariatric cohort
2616 patients treated between 1994 and June 2017
Followed prospectively
11 patients excluded for history of alcohol consumption (>30g/day for men and 20g/day for women
2 patients excluded for HBV
64/2616 (2.4%) patients without liver biopsy at baseline
2350 patients without biopsy-proven NASH
189 patients with NASH
9 patients excluded due to insufficient sample size of liver biospy
189 patients biopsy-proven NASH at time of surgery
- 2 patients died of surgical complications
- 2 gastric banding ablation due to incoercible vomiting
- 1 patient followed in another center
- 3 patients were lost of follow-up
3 patients did not reach 1 year follow-up at time of analysis
125/169 (74%) patients with liver biopsy at 1 year
44*/169 without liver biopsy
- 1 patient died of cardiac decompensation before 5 years evaluation
- 1 gastric band ablation after band migration
- 1 patient with follow-up in another medical center
- 6 patients were lost of follow-up
66 patients did not reach 5 years follow-up at time of analysis
64/94 (68%) patients with liver biopsy at 5 years
30**/94 patients without liver biopsy

*Patients without liver biopsy at 1 year:
- 29 refused liver biopsy
- 8 medical contra-indications(#)
- 2 estimated unnecessary by practitioner
- 1 forgotten to be scheduled by practitioner
- 4 miscellaneous reasons

**Patients without liver biopsy at 5 years:
- 11 medical conta-indication(§)
- 19 patients refused liver biopsy

2 pregnancy, 1 psychiatric decompensation, 1 antiplatelets treatment, 2 surgical complications, 1 cancer, 1 gastric ulcer, § 1 pulmonary embolism, 1 cardiac decompensation, 1 myocardalinfarction, 1 psychiatric decompensation, 3 surgerical, 3 anticoagulation therapy, 1 breast cancer.

Figure 1. Study flowchart. HBV, hepatitis B virus.

numbers (%). The semiquantitative NAS score, ranging from 0 to 8, was also described using medians (IQR). Patient characteristics before bariatric surgery (baseline) were described according to the presence of bridging fibrosis (Brunt's/Kleiner's F3) or cirrhosis (F4) without statistical comparisons. We studied within-patient changes in metabolic, biological, and histologic parameters (all continuous or ordinal variables) from baseline to 5 years, from baseline to 1 year, and from 1 to 5 years after bariatric surgery using the Wilcoxon's signed rank tests for ordinal variables or continuous variables when the change was not normal, or using the paired Student *t* test otherwise. We calculated the rate (with a 95% confidence interval [CI]) of improvement, defined as a decrease of ≥1 points (grade) compared with the baseline value for each semiquantitative score. We compared the rate of disappearance of NASH between patients with mild vs moderate or severe NASH at baseline using the Fisher's exact test.

The exploratory analysis compared the baseline characteristics (BMI and biological and histologic parameters) of patients with persistent and nonpersistent NASH 5 years after surgery using the Mann-Whitney *U* test for ordinal variables and continuous variables with a non-normal distribution, or the Student *t* test otherwise. The 5-year changes in BMI, in NAS, and in the progression of fibrosis were compared using an analysis of covariance adjusted for baseline values. Statistical testing was performed at the 2-tailed a level of .05. Data were analyzed using NCSS 9 software (NCSS, Kaysville, UT).

Results

Cohort Patients

Of the patients enrolled in the Lille bariatric cohort at analysis, 180 presented with liver specimen-proven NASH at surgery (Figure 1). This NASH cohort mainly included women, mean age of 46.7 years, with a median fibrosis score of 2 (IQR, 1–3). Patient characteristics are summarized in Table 1. The main surgical procedure was gastric bypass (66.1%) (Supplementary Table 1).

During the 5-year follow-up, 3 patients died of nonliver-related causes, including 2 deaths from surgical complications within the first month after surgery and 1 from cardiac dysfunction 4 years after surgery.

A histologic evaluation was performed in 74% (125 of 169) of patients at the 1-year follow-up and in 68% (64 of 94) at the 5-year follow-up. The main reason the histologic evaluation was not available in most patients was biopsy refusal (Figure 1). Patients without liver biopsy after bariatric surgery were not significantly different from those with a histologic follow-up except for a lower BMI at 1 year (Supplementary Tables 2–4). Baseline fibrosis did not influence the probability of undergoing histological re-evaluation at 5 years (66% in F3–F4 patients vs 70% in F0–F2 patients, $P = .65$).

Primary Outcome: Resolution of NASH Without Worsening of Fibrosis From Baseline to 5 Years

The resolution of NASH with no worsening of fibrosis occurred in 84.4% (n = 64; 95% CI, 73.1%–92.2%) of patients 5 years after bariatric surgery ($P < .001$) (Figure 2). Improvement was observed in all of the histologic components of NASH (Table 2). The NAS decreased from a median of 5 (IQR, 4–5) to 1 (IQR, 0–2; $P < .001$). The NAS improved by at least 2 points in 90.6% (n = 64; 95% CI, 80.7.2%–96.5%) of patients. Hepatocellular ballooning improved in 87.5% (n = 64; 95% CI, 76.8%–94.4%) and lobular inflammation in 59.4% (n = 64; 95% CI, 46.4%–71.5%) of patients. Resolution of NASH at 5 years was not influenced by the baseline severity of NASH (84% in moderate and severe vs 85% in mild NASH, $P = .9$) or fibrosis (83.3% in F3–F4 vs 86.3% in <F3, $P = .9$).

At 5 years after surgery, the BMI was reduced by ≤5% in 11.3% of patients, by between 5% and 10% in 27.4% of patients and by >10% in 61.3%. The extent of weight loss influenced the rate of resolution of NASH without the worsening of fibrosis at 5 years (primary outcome) (Graphical abstract figure). The median BMI loss in the cohort was 12 kg/m^2, which was significantly associated with NASH resolution without the worsening of fibrosis at 5 years. Indeed, patients with a BMI loss ≥12 kg/m^2 had a higher probability of achieving the primary end point than those with a BMI loss <12 kg/m^2: 93% vs 73% ($P < .0001$).

A subgroup analysis of gastric banding compared with gastric bypass found gastric bypass was significantly more effective in achieving the primary end point ($P = .03$). (Comparison detailed in Supplementary Tables 5 and 6.)

Secondary Outcomes

Evolution of fibrosis at 5 years. Fibrosis improved at 5 years in 70.2% (n = 57; 95% CI, 56.6%–81.6%) of the patients with baseline fibrosis (≥F1). The median fibrosis score decreased from a baseline of 1.5 (IQR, 1–3) to 0 (IQR, 0–1) at 5 years ($P < .001$) (Table 2.). Detailed data on the regression of fibrosis are provided in Table 2 and Figure 3. Moreover, 68.2% (n = 22; 95% CI, 45.1%–86.1%) of patients with ≥F3 fibrosis at baseline had <F3 fibrosis at 5 years.

The disappearance of fibrosis (defined as F0 score) in patients with baseline fibrosis (F ≥1) was observed in 56.1% (n = 57; 95% CI, 42.4%–69.3%) of patients at 5 years. Patients with a fibrosis score of ≤F3 at baseline were more likely to present with the disappearance of fibrosis than those with F3–F4 at baseline: 62.9% (n = 35; 95% CI, 44.9%–78.5%) vs 45.5% (n = 22; 95% CI, 24.4%–67.8%; $P = .07$), respectively. Details of the evolution of fibrosis according to baseline fibrosis (F0 to F4) are provided in Table 3.

We performed a supplementary analysis to study the progression of the noninvasive aspartate aminotransferase-to-platelet ratio index (APRI) score from baseline to 5 years in a larger population (86 of 94 of the cohort [91%] at 5 years). Our analysis showed that the APRI score was significantly reduced from baseline to 5 years and improved from 0.28 (IQR, 0.20–0.43) to 0.17 (IQR, 0.13–0.26; $P < .001$; n = 86). Furthermore, patients without resolution of NASH had higher APRI scores than those without NASH: APRI 0.35 (IQR, 0.17–0.63) vs 0.16 (IQR, 0.12–0.22; $P = .014$).

Table 1. Characteristics of the Cohort

Variable		Fibrosis (Kleiner's score)		
Characteristics	Overall (N = 180)	<F3 (n = 118)[a]	≥F3 (n = 58)[a]	F4 (n = 9)[a]
Women	116 (66)	77 (65)	39 (67)	6 (66)
Age, y	46.7 ± 10.6	46.1 ± 10.5	47.5 ± 10.8	50.9 ± 5.8
BMI, kg/m^2	48.1 ± 7.9	48.2 ± 7.7	48.3 ± 6.9	46 ± 6.5
BMI at age 20 y, kg/m^2	29.5 ± 7.4	30.1 ± 8.3	29 ± 6.6	29.6 ± 4.4
Diabetes	128 (71)	77 (65)	48 (83)	7 (78)
Arterial hypertension	137 (76)	87 (74)	47 (81)	6 (66)
Biological features				
HDL cholesterol, *mmol/L*	1.1 (0.9–1.2)	1.0 (0.9–1.3)	1.1 (0.9–1.2)	1.0 (0.8–1.2)
LDL cholesterol, *mmol/L*	3 (2.2–3.4)	3 (2.4–3.4)	2.8 (2.1–3.7)	2.8 (1.3–4.1)
Triglycerides, *mmol/L*	1.8 (1.3–2.5)	1.8 (1.3–2.4)	1.8 (1.3–2.6)	2 (1.2–2.6)
Total cholesterol, *mmol/L*	5 (4.2–5.6)	5 (4.3–5.5)	4.6 (4.2–5.8)	4.8 (3.2–6.2)
AST, *IU/L*	36 (28–49)	34 (27–41)	49 (32–61)	49 (33–62)
ALT, *IU/L*	45 (33–62)	42 (32–56)	51 (36–68)	45 (34–58)
GGT, *IU/L*	56 (39–96)	50 (34–76)	82 (37–135)	106 (50–170)
Bilirubin, *mg/dL*	4 (3–6)	4 (3–6)	4.9 (3.7–6)	4.5 (3.7–6.5)
Fasting glucose, *mg/dL*	136(102–191)	124(100–178)	152(112–221)	167(124–213)
Insulin resistance index[b]	3.5 (3.3–3.7)	3.4 (3.2–3.6)	3.6 (3.4–3.9)	3.7 (3.3–4.0)
Hemoglobin A_{1c}, %	7.3 (6–8.9)	6.9 (5.9–8.9)	7.7 (6.3–8.9)	7.9 (6.5–8.6)
Albumin, *g/L*	42.8 ± 2.9	43 ± 2.9	42 ± 2.9	41.6 ± 1.8
Platelets, *G/L*	258 ± 63	253 ± 60	252 ± 71	218 ± 62
Prothrombin time, %	96 ± 5.5	97 ± 5.4	94 ± 5.6	96.5 ± 5.4
Histologic features				
Biopsy length, *mm*	14 (10–16)	14 (10–17)	13.5 (10–15)	13.5 (10–17)
Portal triads	9 (7–10)	9 (7–10)	9 (7–11)	7 (6–8)
NAS score	5 (4–5)	5 (4–5)	5 (4.8–6)	5 (4.5–6)
Steatosis, %	60 (40–75)	60 (40–75)	60 (39–80)	50 (30–75)
Steatosis >60%	102 (56.7)	68 (58)	32 (55)	4 (44)
Brunt's score				
1	121 (67)	93 (79)	26 (45)	1 (11)
2	46 (26)	23 (19)	21 (36)	5 (56)
3	13 (7)	2 (2)	11 (19)	3 (33)
Ballooning				
0	4 (2.2)			
1	114 (63.3)			
2	62 (34.5)			
Lobular inflammation				
0	9 (5)			
1	119 (66.1)			
2	48 (26.7)			
3	4 (2.2)			
Fibrosis (Kleiner's score)[a]				
0	30 (17)			
1a	22			
1b	15			
1c	14			
1	2			
Total	53 (30)			
2	35 (20)			
3	49 (28)			
4	9 (5)			

NOTE: Categorical data are presented as n (%) and continuous data as the mean ± SD or median (IQR).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; $HbA_{1c,}$ glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]4 liver biopsy specimens were of insufficient quality to properly quantify fibrosis.
[b]Insulin resistance was obtained with the formula (1/QUICKI).

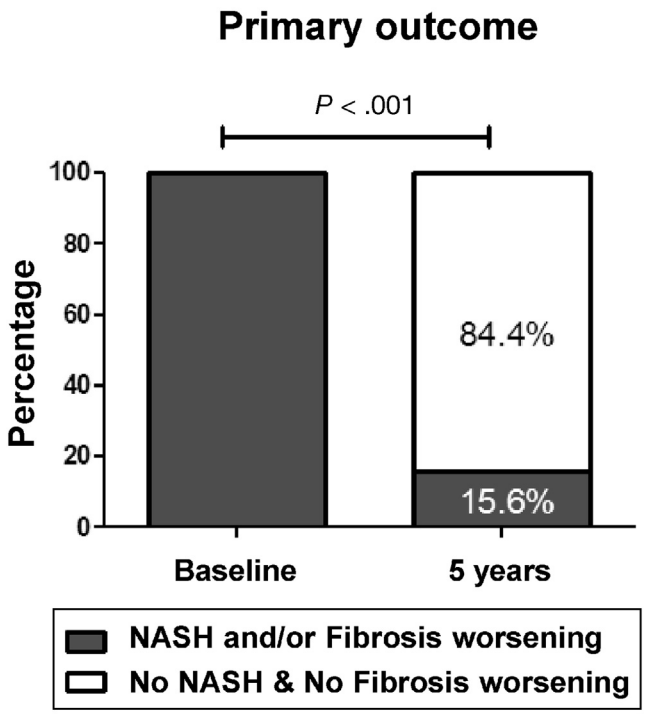


Figure 2. A histogram shows resolution of NASH without worsening of fibrosis at 5 years after bariatric surgery (n = 64 patients). Paired biopsy analysis. Statistical analysis: Paired Wilcoxon's signed rank test. Diagnosis and resolution of NASH was defined by the pathologist.

Evolution according to the resolution or persistence of NASH at 5 years. Patients with persistent NASH or a worsening of fibrosis, or both, had a less favorable response to bariatric surgery with less weight loss after adjustment for baseline BMI than those without NASH (BMI -6.3 ± 4.1 kg/m^2 vs -13.4 ± 7.4 kg/m^2, $P = .017$, respectively) and thus a higher BMI at 5 years (40.9 ± 10.7 kg/m^2 vs 35.3 ± 7.1 kg/m^2, $P = .03$, respectively) (Table 4). Patients with persistent NASH had more severe histologic lesions at 5 years than those without NASH: median fibrosis 2 (IQR, 1.3–3) vs 0 (IQR, 0–1; $P < .001$), median NAS 4 (IQR, 3.5–5.5) vs 1 (IQR, 0–2; $P < 0.001$) and steatosis 60% (IQR, 30%–75%) vs 5% (IQR, 1%–20%; $P < .001$, respectively) (Table 4).

The disappearance of NASH alone, without taking into consideration the worsening of fibrosis, was associated with an improvement in fibrosis of -1 (IQR, 0 to -2) vs 0 (IQR, 0 to 2; $P = .019$; adjusted with baseline fibrosis).

Patients with persistent NASH had more biological abnormalities: aspartate aminotransferase, 43 IU/L (IQR, 33–63 IU/L) vs 20 IU/L (IQR, 17–24 IU/L); alanine aminotransferase, 46 IU/L (IQR, 33–52 IU/L) vs 18 IU/L (IQR, 17–25 IU/L); and γ-glutamyltransferase, 72 IU/L (IQR, 25–146 IU/L) vs 18 IU/L (IQR, 12–28 IU/L; $P < .01$ for all); and insulin resistance (1/QUICKI) 3.5 (IQR, 3.1–4.1) vs 2.9 (IQR, 2.7–3.1; $P = .01$) (Table 4).

Evolution of histologic features during the 5 years of follow-up. At 1 year after surgery, NASH resolved in 84% (n = 125; 95% CI, 76.4%–89.9%) of patients ($P < .001$). The Brunt's necroinflammation severity scale improved ($P < .001$) (Supplementary Table 7). Median fibrosis was significantly reduced: 2 (IQR, 1–3) vs. 1 (IQR, 0–2; $P < .001$). All of the histologic features of NASH improved, including hepatocellular ballooning, lobular inflammation, and steatosis (Supplementary Table 7 and Supplementary Figure 1).

There was no difference in the resolution of NASH ($P = .17$) between the 1- and 5-year follow-up (Supplementary Figure 1).

Unlike the necroinflammatory process, fibrosis continued to improve between the 1- and 5-year follow-up ($P < .001$) with a decrease that began at 1 year ($P < .001$) (Supplementary Tables 7 and 8).

Evolution of clinical and biological features during the 5 years of follow-up. Clinical and biological parameters, except for total bilirubin, albumin, low-density lipoprotein cholesterol, prothrombin time, and platelets, improved within the first year. These improvements were maintained at the 5-year follow-up (Table 2; Supplementary Tables 7 and 8). The degree of weight loss influenced the metabolic response after surgery. A BMI loss of more than 10% was associated with greater improvement in the metabolic outcome. (Supplementary Table 9). Weight regain is a main issue after bariatric surgery. However, the small sample size of our cohort made it impossible to analyze its impact on the persistence of NASH at 5 years.

Discussion

In this long-term prospective study with consecutive liver biopsies, bariatric surgery induced the resolution of NASH without worsening of fibrosis in 84% of patients at 5 years. Long-term resolution of NASH led to the regression of fibrosis in 70% of patients. The resolution of NASH occurred within the first year and was maintained over the 5-year period, whereas fibrosis began to improve within 1 year and continued throughout the 5-year follow-up.

With an 80% success rate for the resolution of NASH without worsening of fibrosis, bariatric surgery could be considered as a therapeutic option for morbidly obese patients. Most patients improved within 1 year after treatment. Very few recurrences were observed between 1 and 5 years. An absolute change in liver fat content, lobular inflammation, and hepatocellular ballooning was observed in most patients as well as a decrease of 2 points or more in the NAS score. The long-term benefits suggest the notion of disease remission. NASH remission should be considered in relation to the remission of diabetes and the metabolic syndrome, which have already been described after bariatric surgery. Thus, effects of bariatric surgery go beyond NASH and provide a global metabolic benefit. As shown for refractory diabetes, bariatric surgery should be evaluated in NASH patients with mild obesity (BMI <35 kg/m^2) and advanced fibrosis.

Fibrosis is the most reliable predictor of liver-related mortality. Its improvement is an important end point (recommended by the United States Food and Drug Administration) in clinical trials.[3] In our study, improvement of fibrosis (70% of patients at 5 years) was gradual and regular, beginning in the first year and continuing throughout the 5 years of follow-up. In patients with baseline bridging fibrosis ($\geq$F3), fibrosis improved and even disappeared at 5 years in 68% and 45% of patients,

Table 2. Evolution of Clinical, Biological, and Histologic Features Between Baseline and 5 Years After Bariatric Surgery

Characteristics	Paired values analysis		
	Before surgery	5 years after surgery	*P* value
BMI, *kg/m²*	48.1 ± 6.9	36.1 ± 7.8	<.001
Biological characteristics			
HDL cholesterol, *mmol/L*	1.1 (0.9–1.3)	1.3 (1.2–1.5)	<.001
LDL cholesterol, *mmol/L*	2.7 (2.2–3.4)	2.8 (2.4–3.4)	.36[b]
Triglycerides, *mmol/L*	1.6 (1.3–2.4)	1.1 (0.7–1.6)	<.001[a]
Total cholesterol, *mmol/L*	4.9 (4.1–5.4)	4.6 (4.1–5.3)	.64[b]
AST, *IU/L*	36 (27–50)	21 (18–26)	<.001[a]
ALT, *IU/L*	47 (36–65)	19 (13–30)	<.001[a]
GGT, *IU/L*	50 (38–77)	20 (13–39)	<.001[a]
Bilirubin, *mg/dL*	0.5 (0.4–0.6)	0.5 (0.4–0.6)	.86[a]
Fasting blood glucose, *mg/dL*	132 (92–192)	105 (89–123)	<.001[a]
Insulin resistance index[c]	3.4 (3.3–3.6)	2.9 (2.7–3.1)	<.001[a]
HbA_{1c}, %	7.5 (6–8.8)	5.9 (5.5–6.5)	<.001[a]
Albumin, *g/L*	42.9 ± 2.7	42.5 ± 3.6	.41[b]
Platelets, *G/L*	249 ± 63	241 ± 57	.19[b]
Prothrombin time, %	95.8 ± 6.0	95.1 ± 6.6	.37[b]
Histologic characteristics			
Steatosis, %	60 (50–74)	6 (1–20)	<.001[a]
Brunt's score			<.001[a]
0	0	58	
1	43	3	
2	15	2	
3	6	1	
Ballooning[d]			<.001[a]
0	3	55	
1	36	6	
2	25	3	
Lobular inflammation[d]			<.001[a]
0	5	38	
1	45	23	
2	13	3	
3	1	0	
Fibrosis (Kleiner's score)[d]			,001[a]
0	7	39	
1a	12	3	
1b	5	2	
1c	7	5	
1	1	1	
Total	25	10	
2	10	6	
3	19	7	
4	3	2	

NOTE: Continuous data are presented as the mean ± SD or median (IQR) and categorical data as the number of patients.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltranspeptidase; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Wilcoxon's signed rank test.
[b]Paired Student *t* test.
[c]Insulin resistance index was obtained with the formula (1/QUICKI).
[d]Paired histologic characteristics could be evaluated for 64 patients between baseline and 5 year after surgery.

respectively. The pathophysiological mechanism of fibrolysis continues long after suppression of the necroinflammatory process. Such phenomenon has also been described after viral suppression in hepatitis B and C. These data support the notion that bariatric surgery could reduce liver-related mortality. Broad cohort studies are still required to evaluate survival and to clarify the causes of worsening fibrosis, especially in patients with baseline F3/F4 fibrosis.

We found 20% of patients were nonresponders to surgery and had persistent NASH at 5 years. NASH was already present in most of them at 1 year, suggesting that the persistent disease at 5 years was more likely due to an early phenomenon rather than recurrent disease during follow-

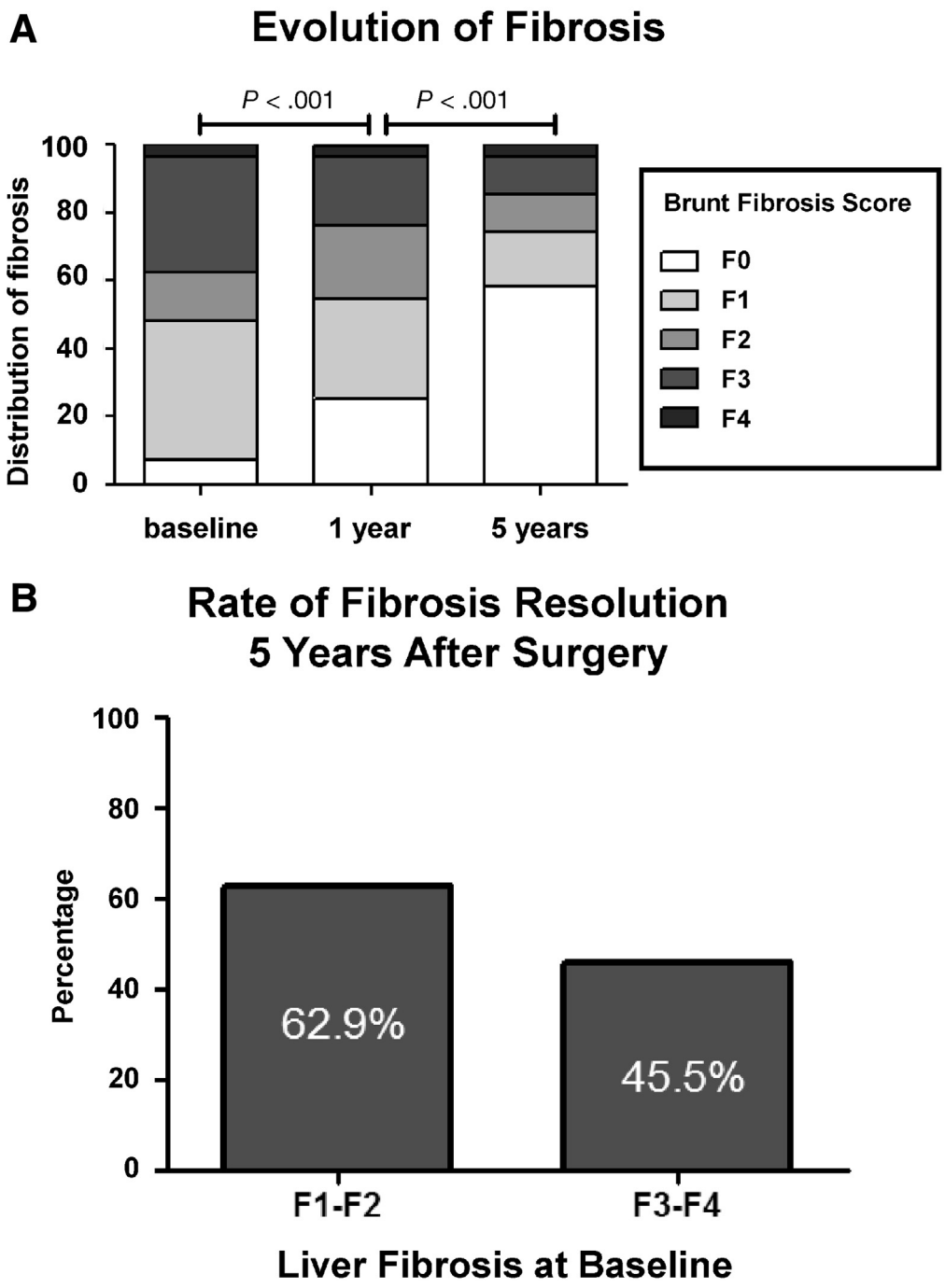


Figure 3. (*A*) Evolution of fibrosis after surgery: Histogram represents the fibrosis distribution according to Brunt's Fibrosis score at baseline, 1 year, and 5 years. (Only patients with available biopsy specimens at each time point are represented.) Statistical analysis: Paired Wilcoxon's signed rank test. (*B*) Resolution of fibrosis after surgery: Histogram represents the rate of fibrosis resolution at 5 years. Fibrosis resolution is defined by a F0 fibrosis score of Brunt's scale on liver histology at 5 years.

up. Low weight loss and less improvement in insulin resistance were associated with failing to reach the primary end point. Identifying predictive factors of success/failure as early as possible seems necessary to propose alternative therapeutic strategies. Concerning the choice of surgical procedures, no recommendations can be given because the study was not planned to compare their efficacy (sample size and the study design were not adapted). This question is still a main issue and requires further studies.

Long-term data on the histologic effects of medical or surgical treatment on NASH are lacking. The prospective design of our study with sequential liver biopsies limits bias. Moreover, although biopsies were not performed in a certain number of patients, the absence of significant differences between patients with or without liver sample strongly supports the hypothesis that biopsy refusal did not result in bias.

Secondly, 68% of patients had available liver biopsy specimens, a high rate compared with previous studies showing the long-term regression of fibrosis in patients treated for hepatitis B virus.[24] In addition, the identical histologic results observed at 1 year in the present study and those in our previous study in a smaller cohort suggest that our data are robust.[17]

Table 3. Evolution of Fibrosis From Baseline to 5 Years After Bariatric Surgery

	Brunt's fibrosis score, 5 years after bariatric surgery					
Brunt's fibrosis score at baseline	0	1	2	3	4	Total
0	7	0	0	0	0	7
1	14	6	3	2	0	25
2	8	1	1	0	0	10
3	10	3	2	3	1	19
4	0	0	0	2	1	3
Total	39	10	6	7	2	64

Prevalence of NASH varies widely among studies, and our prevalence may seem to be low.[25,26] It is possible that biopsies may have been mainly performed in patients with suspected liver injury in some studies without a systematic liver biopsy protocol.

Finally, our selection process may have decreased the prevalence of NASH at bariatric surgery because patients have been required to follow a strict nutritional medical program since 2006. Exclusion of patients who did not complete the program could have influenced the prevalence of NASH.

Furthermore, the length of the liver specimen could be considered a limitation because certain experts recommend a length of 2 to 3 cm. However, we used a conservative approach to biopsies and requested that they be at least 8 mm long, which is longer than the minimal length proposed by expert guidelines. Needle biopsy was used to ensure good-quality specimens, thus avoiding the risk of

Table 4. Patients With Resolution of NASH Without Worsening of Fibrosis (Meeting Primary Outcome) Compared With Those With Persistent NASH or Worsening of Fibrosis at 5 Years, or Both

Characteristics of patients at 5 years	Resolution of NASH without worsening of fibrosis	Persistence of NASH and/or worsening of fibrosis	*P* value
Baseline BMI, *kg/m²*	49.3 ± 7.0	47.7± 7.9	.86
BMI at 5 years, *kg/m²*	35.3 ± 7.1	40.9 ± 10.7	.028[a]
Evolution of BMI	−13.4 ± 7.4	− 6.3 ± 4.1	.017[a]
Histological characteristics			
Brunt's fibrosis score	0 (0–1)	2 (2–3)	<.001[b]
Brunt's fibrosis evolution	−1 (0 to −2)	1 (0–1.3)	.003[b]
NAS	1 (0–2)	4 (3.5–5.5)	<.001[b]
NAS evolution	−4 (−5 to −2)	0 (−2 to 0)	.005[b]
Steatosis, %	5 (1–10)	60 (30–75)	<.001[b]
Biological characteristics			
Fasting glucose, *mg/dL*	104 (89–117)	128 (85–165)	.17[b]
HbA_{1c}, %	5.8 (5.5–6.4)	6.8 (5.5–7.5)	.21[b]
Insulin resistance index[c]	2.9 (2.7–3.1)	3.5 (3.1–4.1)	.001[b]
AST, *IU/L*	20 (17–24)	43 (33–63)	<.001[b]
ALT, *IU/L*	18 (17–25)	46 (33–52)	.010[b]
GGT, *IU/L*	18 (12–28)	72 (25–146)	<.001[b]
Total bilirubin, *mg/dL*	0.5 (0.4–0.5)	0.7 (0.4–1)	.10[b]
LDL cholesterol, *mmol/L*	2.7 (2.4–3.2)	3.3 (2.2–5.0)	.46[b]
HDL cholesterol, *mmol/L*	1.4 (1.2–1.5)	1.3 (1.0–1.6)	.58[b]
Triglycerides, *mmol/L*	1 (0.7–1.6)	1.6 (1.3–2.2)	.037[b]
Albumin, g/L	42 ± 3	44 ± 4	.51[a]
Platelets, *G/L*	248 ± 51	233 ± 76	.48[a]
Prothrombin time, %	96 ± 7	90 ± 12	.12[a]

NOTE: Data are presented as the mean ± SD or median (IQR).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltranspeptidase; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Paired Student *t* test.
[b]Wilcoxon's signed rank test.
[c]Insulin resistance was obtained with the formula (1/QUICKI).

inflammation associated with a wedge biopsy. Thus, although the length of liver specimen may not be optimal and might be considered a limitation to the study, the quality of the liver biopsy specimen was correct.

Regarding noninvasive assessment of fibrosis, results with the APRI score must be analyzed by considering its limits. Only future studies with an adapted study design could confirm or not the interest of this test in this setting. Up to now, analysis of a liver specimen remains the only validated method to assess fibrosis evolution after bariatric surgery.

The benefits of bariatric surgery on liver histology must be weighed against the risk and safety of surgery. Our study did not have the power and was not designed to perform a safety analysis, and these studies are urgently needed. Thus, bariatric surgery cannot be considered first-line therapy due to the surgical risk.[10] It explains the differences between American and European guidelines on NAFLD,[4,5] with the former considering the data to be too premature to recommend bariatric surgery, whereas the latter suggest that it can be proposed to highly selected patients.

Conclusion

This prospective 5-year follow-up of obese NASH patients showed that the beneficial effects of bariatric surgery on the resolution of NASH were durable and led to a sustained reduction in fibrosis over 5 years.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.06.006.

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Conflicts of interest
The authors disclose no conflicts.

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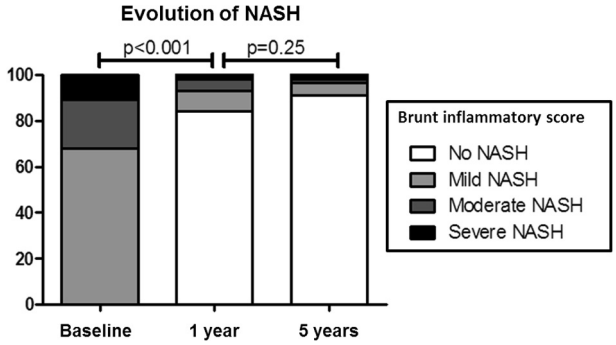

Supplementary Figure 1. Evolution of the necroinflammatory activity of NASH after bariatric surgery. Paired liver biopsy. Statistical analysis by Wilcoxon's signed rank test.

Supplementary Table 1. Bariatric Surgery Procedures According to Baseline Fibrosis Stage

		Fibrosis (Kleiner's score)		
Bariatric procedures	Overall (N = 180)	<F3 (n = 118)[a]	≥F3 (n = 58)[a]	F4 (n = 9)
Gastric band	39 (21.7)	27 (23)	12 (20.7)	1 (11.1)
Gastric bypass	119 (66.1)	76 (64.5)	39 (67.2)	5 (55.6)
Sleeve gastrectomy	21 (11.7)	14 (12)	7 (12.1)	3 (33.3)
Shunt	1 (0.5)	1 (0.5)	0 (0)	0

NOTE: Data are presented as n (%).
[a]4 liver biopsy specimens were of insufficient quality to properly quantify fibrosis.

Supplementary Table 2. Baseline Comparison of Patients With or Without Liver Biopsy 5 Years After Surgery

Characteristics	Liver biopsy	No liver biopsy	*P* value
Age, *y*	46.7 ± 10.2	46.7 ± 11.4	.98[a]
BMI, *kg/m²*	48.7 ± 7.0	46.6 ± 8.0	.10[a]
Fasting glucose, *mg/dL*	137 (100–181)	133 (106–212)	.33[b]
HOMA-IR	3.3 (2.2–5.3)	3.8 (2.2–6)	.80[b]
HbA_{1c}, %	7.2 (6–8.6)	7.6 (6–9)	.39[b]
LDL cholesterol, *mmol/L*	3.0 (2.3–3.4)	2.8 (2.2–3.4)	.35[b]
HDL cholesterol, *mmol/L*	1.1 (0.9–1.2)	1.1 (0.9–1.2)	.83[b]
AST, *IU/L*	35 (28–49)	38 (30–50)	.65[b]
ALT, *IU/L*	44 (34–62)	47 (33–65)	.34[b]
GGT, *IU/L*	51 (37–96)	65 (41–105)	.09[b]
Bilirubin, *mg/dL*	0.4 (0.3–0.6)	0.4 (0.3–0.6)	.74[b]
Steatosis, %	60 (43–75)	60 (40–80)	.68[b]
NAS	5 (4–5)	5 (4–5)	.65[b]
Fibrosis score	2 (1–3)	1 (0–3)	.19[b]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltranspeptidase; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein ; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein.
[a]Paired Student *t* test.
[b]Wilcoxon's signed rank test.

Supplementary Table 3. Comparison at 1 Year of Patients With or Without Liver Biopsy 5 Years After Surgery

Characteristics	Liver biopsy	No liver biopsy	*P* value
BMI, *kg/m²*	36.6 ± 7.4	34.1 ± 6.8	.05[a]
Fasting glucose, *mg/dL*	94 (86–109)	95 (87–113)	.49[b]
HOMA-IR	1 (0.7–1.6)	1.2 (0.9–2)	.27[b]
HbA_{1c}, %	5.7 (5.3–6.4)	5.5 (5.1–6)	.32[b]
LDL cholesterol, *mmol/L*	2.8 (2.2–3.3)	2.6 (2.3–3.1)	.21[b]
HDL cholesterol, *mmol/L*	1.2 (1.0–1.5)	1.3 (1.1–1.5)	.15[b]
AST, *IU/L*	21 (17–27)	24 (20–29)	.89[b]
ALT, *IU/L*	20 (15–28)	22 (17–29)	.94[b]
GGT, *IU/L*	23 (14–38)	20 (12–44)	.41[b]
Bilirubin, *mg/dL*	0.5 (0.4–0.7)	0.5 (0.4–0.7)	.93[b]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltranspeptidase; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein.
[a]Paired Student *t* test.
[b]Wilcoxon's signed rank test.

Supplementary Table 4. Comparison at 5 Years of Patients With or Without Liver Biopsy 5 Years After Surgery

Characteristics	Liver biopsy	No liver biopsy	*P* value
BMI, kg/m^2	36.3 ± 7.4	35.8 ± 8.6	.78[a]
Fasting glucose, *mg/dL*	104 (89–130)	106 (88–123)	.22[b]
HOMA-IR	1.2 (1–2.2)	1.1 (0.7–1.5)	.92[b]
$HbA_{1c,}$ %	5.9 (5.5–6.5)	5.8 (5.5–7.2)	.28[b]
LDL cholesterol, *mmol/L*	2.7 (2.4–3.4)	2.8 (1.9–3.2)	.18[b]
HDL cholesterol, *mmol/L*	1.3 (1.2–1.5)	1.4 (1.1–1.6)	.70[b]
AST, *IU/L*	21 (17–26)	24 (17–34)	.87[b]
ALT, *IU/L*	19 (13–29)	19 (15–22)	.83
GGT, *IU/L*	20 (13–38)	27 (10–48)	.41
Bilirubin, *mg/dL*	0.5 (0.4–0.6)	0.4 (0.3–0.6)	.09

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltranspeptidase; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein.
[a]Paired Student *t* test.
[b]Wilcoxon's signed rank test.

Supplementary Table 5. Comparison of Baseline Characteristics According to Surgical Procedure

Characteristics	Gastric bypass	LAGB	*P* value[a]
Sex, % *male*	37	31	.5
Age, *y*	46.1 (39.1–53.6)	50.7 (37.2–56.4)	.1
BMI, kg/m^2	48.4 ± 8	46.4 ± 6.1	.2
Fasting glucose, *mg/dL*	143 (103–200)	119 (91–175)	.2
Insulin resistance value, *(1/QUICKI)*	3.5 (3.5–3.7)	3.4 (3.1–3.8)	.9
HbA_{1c}, %	7.5 (6–8.95)	6.9 (5.9–9.2)	.5
Total cholesterol, *mmol/L*	4.9 (4.2–5.5)	4.9 (4.1–5.5)	.8
LDL cholesterol, *mmol/L*	3 (2.2–3.5)	2.9 (2–3.4)	.9
HDL cholesterol, *mmol/L*	1.1 (0.9–1.3)	1.1 (1–1.3)	.4
Triglycerides, *mmol/L*	1.8 (1.3–2.5)	1.8 (1.4–2.6)	.8
AST, *IU/L*	37 (28–49)	35 (29–50)	.8
ALT, *IU/L*	46 (33–64)	44 (33–65)	.6
GGT, *IU/L*	56 (41–100)	51 (34–86)	.2
Total bilirubin, *mg/dL*	0.4 (0.3–0.6)	0.4 (0.3–0.6)	.7
Platelets, *G/L*	254 (214–297)	253 (218–286)	.6
NAS	5 (4–5)	5 (4–6)	.1
Steatosis, %	60 (30–80)	70 (50–75)	.2
Fibrosis >2 (Brunt's score), %	34	31	.7

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltranspeptidase; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; LAGB, laparoscopic gastric banding; LDL, low-density lipoprotein.
[a]Comparison between LAGB and Roux-en-Y Gastric Bypass. Statistical methods: median analysis with Kruskal-Wallis, mean analysis with Terry-Hoeffding when expected normal scores, and proportion analysis with Pearson's χ^2 test. Statistical significance: $P < .05$.

Supplementary Table 6. Comparison of Gastric Bypass and Laparoscopic Gastric Banding Efficacy 5 Years After Surgery

Characteristics	LAGB	Roux-en-Y gastric bypass	*P* value[a]
No NASH and no fibrosis worsening	68.4	90.2	.03
NAS ≥3	33.3	66	.003
Steatosis, %	10 (1–60]	5 (1–17.5]	.18
Fibrosis	1 (0–2)	0 (0–1)	.08
BMI loss, kg/m^2	10.8 ± 9.5	12.7 ± 5.7	.07
Biological			
Fasting glucose, *mg/dL*	106 (87–126)	103 (89–124)	.88
HbA_{1c}, %	5.7 (5.3–7.3)	6 (5.6–6.6)	.60
Insulin resistance *(1/QUICKI)*	2.9 (2.7–3.4)	2.9 (2.7–3.1)	.62
Total cholesterol, *mmol/L*	4.7 (4.3–5.4)	4.6 (3.9–5.3)	.33
LDL cholesterol, *mmol/L*	2.8 (2.4–3.5)	2.7 (2.3–3.3)	.14
HDL cholesterol, *mmol/L*	1.3 (1.1–1.5)	1.4 (1.2–1.6)	.19
Triglycerides, *mmol/L*	1.2 (0.8–1.9)	1.1 (0.7–1.5)	.27
AST, *IU/L*	23 (17–32)	23 (18–30)	.96
ALT, *IU/L*	20 (13–31)	20 (16–25)	.93
GGT, *IU/L*	27 (16–58)	19 (11–28)	.04
Total bilirubin, *mg/dL*	0.5 (0.3–0.6)	0.4 (0.3–0.6)	.92

NOTE: Categorical data are presented as the percentage of patients and continuous data as the median (IQR) or mean ± SD.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltranspeptidase; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; LAGB, laparoscopic gastric banding; LDL, low-density lipoprotein.
[a]Statistical tests: Mann-Whitney test for nonparametric parameters and Terry-Hoeffding for expected normal scores.

Supplementary Table 7. Evolution of Clinical, Biological, and Histologic Features Between Baseline and 1 Year After Bariatric Surgery

Characteristics	Paired values analysis		
	Before surgery	1 year after[a] surgery	*P* value
BMI, kg/m^2	48.3 ± 7.9	35.9 ± 7.3	<.001[b]
Biological characteristics			
HDL cholesterol, *mmol/L*	1.1 (0.9–1.2)	1.2 (1.0–1.5)	<.001[c]
LDL cholesterol, *mmol/L*	3.0 (2.3–3.4)	2.8 (2.2–3.3)	.11[c]
Triglycerides, *mmol/L*	1.8 (1.3–2.4)	1.24 (0.9–1.7)	<.001[c]
Total cholesterol, *mmol/L*	5 (4.2–5.6)	4.6 (4.1–5.3)	.015[c]
AST, *IU/L*	35 (28–49)	21 (17–27)	<.001[c]
ALT, *IU/L*	44 (34–62)	20 (15–28)	<.001[c]
GGT, *IU/L*	51 (37–96)	23 (14–37)	<.001[c]
Bilirubin, *mg/dL*	0.4 (0.3–0.6)	0.5 (0.4–0.7)	<.001[c]
Fasting blood glucose, *mg/dL*	134(100–181)	94 (86–109)	<.001[c]
Insulin resistance index	3.5 (3.3–3.7)	2.9 (2.7–3.1)	<.001[c]
HBA_{1c}, %	7.2 (6–8.6)	5.7 (5.3–6.4)	<.001[c]
Albumin, *g/L*	43 ± 2.8	43 ± 2.7	.27[b]
Platelets, *G/L*	258 ± 62	254 ± 62	.29[b]
Prothrombin time, %	96 ± 5.3	93 ± 9.5	<.001[b]
Histologic characteristics			
Brunt's score			<.001[b]
0 (no NASH)	0	105	
1	82	13	
2	33	6	
3	10	1	
Steatosis, %	60 (42.5–75)	10 (1–25)	<.001[b]
Ballooning			<.001[b]
0	2	93	
1	79	19	
2	44	13	
Lobular inflammation			<.001[b]
0	6	72	
1	85	46	
2	32	5	
3	2	2	
Fibrosis (Kleiner's/Brunt's)[a]			<.001[b]
0	14 (12.5)	40 (35)	
1a	17	8	
1b	10	5	
1c	10	18	
1	1	2	
Total	36 (31.6)	33 (26.7)	
2	26 (21)	17 (14.1)	
3	38 (31.6)	27 (21.7)	
4	4 (3.3)	3 (2.5)	

ALT, alanine aminotransferase; AST aspartate aminotransferase; GGT, γ-glutamyltranspeptidase; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a]Fibrosis could not be evaluated for 5 patients at month 0 or at month 12 due to the quality of the histologic sample (number of portal triads) (N = 120, paired biopsy specimens).

[b]Paired Student t test.

[c]Wilcoxon's signed rank test.

Supplementary Table 8. Evolution of Clinical, Biological, and Histologic Features Between 1 and 5 Years After Bariatric Surgery

Characteristics	Paired value analysis		
	1 year after surgery	5 years after surgery	*P* value
BMI, *kg/m²*	36.8 ± 6.5	36.0 ± 7.6	.36[a]
Biological characteristics			
Fasting glucose, *mg/dL*	95 (86–114)	105 (89–123)	.004[b]
Insulin resistance index	2.8 (2.7–3)	2.9 (2.7–3.1)	.20[b]
HbA_{1c}, %	5.7 (5.4–6.5)	5.9 (5.5–6.5)	.21[b]
Triglycerides, *mmol/L*	1.2 (0.8–1.7)	1.1 (0.7–1.6)	.12[b]
HDL cholesterol, *mmol/L*	1.3 (1.1–1.5)	1.3 (1.2–1.5)	.12[b]
LDL cholesterol, *mmol/L*	2.6 (2.1–3.4)	2.8 (2.4–3.4)	.007[b]
AST, *IU/L*	20 (17–26)	21 (18–26)	.40[b]
ALT, *IU/L*	19 (15–26)	19 (13–30)	.28[b]
GGT, *IU/L*	21 (14–33)	20 (13–39)	.73[b]
Bilirubin, *mg/dL*	0.6 (0.4–0.7)	0.5 (0.4–0.6)	.002[b]
Albumin, *g/L*	42 ± 2.8	42.3 ± 3.6	.34[a]
Platelets, *G/L*	250 ± 55	244 ± 54	.35[a]
Prothrombin time, %	93 ± 9.6	95 ± 7.2	.08[a]
Histologic characteristics			
Steatosis, %	10 (3–30)	6 (1–20)	.06[b]
Brunt's inflammatory scale	0 (0–0)	0 (0–0)	.25[b]
Brunt's fibrosis score	1 (0–2.8)	0 (0–1)	<.001[b]

AST, aspartate aminotransferase; ALT, alanine aminotransferase; **G**GT, γ-glutamyltranspeptidase; HDL, high-density lipoprotein; HbA_{1c}, glycated hemoglobin, LDL, low-density lipoprotein.
[a]Paired Student *t* test.
[b]Wilcoxon's signed rank test.

Supplementary Table 9. Liver and Metabolic Outcome According to the Weight Loss

Characteristics	0–5 kg/m²	5–10 kg/m²	*P* value[a]	>10 kg/m²	*P* value[b]
Fasting glucose, *mg/dL*	118 (94–180)	122(102–140)	0.9	95 (87–112)	<.001
HbA_{1c} %	6.6 (5.6–8.3)	6.5 (5.7–7.4)	0.8	5.7 (5.3–6.1)	<.001
Insulin resistance, 1/QUICKI	3.2 (3–3.6)	3.3 (3–3.4)	0.4	2.8 (2.6–3)	<.001
Triglycerides, *mmol/L*	1.6 (1.1–2.6)	1.6 (1.1–2.6)	1	0.9 (0.7–1.2)	<.001
Total cholesterol, *mmol/L*	4.5 (4.1–5.1)	5 (3.8–5.8)	0.7	4.6 (4.1–5.4)	.3
LDL cholesterol, *mmol/L*	2.6 (2.4–3.1)	3.0 (2.5–3.5)	0.7	2.7 (2.3–3.3)	.5
HDL cholesterol, *mmol/L*	1.3 (1.1–1.4)	1.2 (1.1–1.4)	0.7	1.4 (1.2–1.6)	.01
AST, *IU/L*	24 (15–40)	26 (20–38)	0.5	20 (17–24)	.004
ALT, *IU/L*	30 (14–46)	23 (18–38)	0.8	16 (21–12)	<.001
GGT, *IU/L*	30 (26–76)	27 (21–57)	0.7	16 (11–28)	<.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltranspeptidase; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Statistical test: Kruskal-Wallis test (variance of median), statistical significance defined by $P < .05$.
[a]Comparison between the group 0–5 kg/m² and the group 5–10 kg/m².
[b]Comparison between the group 5–10 kg/m² and the group >10 kg/m².